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(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: WILLIAMS, Alfred, Glyn [GB/GB]; 1 Pitts Close, Emmets Park, Binfield, Berkshire RG12 5ES (GB).

(74) Agents: BISHOP, Nigel, Douglas et al.; ZENECA Agrochemicals, Intellectual Property Dept., Jealott's Hill Research Station, P.O. Box 3538, Bracknell, Berkshire RG42 6YA (GB).

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(54) Title: PROCESS FOR THE PREPARATION OF 4-BROMO-1,1-DIFLUOROBUT-1-ENE AND 2,4-DIBROMO-1,1,1-TRIFLUOROBUTANE

(57) Abstract

A process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the step of reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass and recovering the desired product therefrom. The product is useful as an intermediate for pesticidal compounds.

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PROCESS FOR THE PREPARATION OF 4-BROMO-1,1-DIFLUOROBUT-1-ENE AND 2,4-DIBROMO-1,1,1-TRIFLUOROBUTANE

The present invention relates to a novel process for the preparation of 4-bromo-1,1-difluorobut-1-ene. The present invention also relates to a novel process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane.

4-bromo-1,1-difluorobut-1-ene is a useful compound in many fields of activity such as agrochemicals and fluoro polymers, both as an end product and particularly as an intermediate.

International Patent Application Publication Nos. WO94/06777, WO94/06782, WO95/24403 and WO96/00003 disclose a series of heterocyclic derivatives having a 4,4-difluorobut-3-enylthio substituent, which are useful as nematicides, and methods of preparing them. These methods involve a reaction step with 4-bromo-1,1-difluorobut-1-ene. It is proposed to prepare 4-bromo-1,1-difluorobut-1-ene by reacting hydrogen bromide with the commercially available compound 4-bromo-1,1,2-trifluorobut-1-ene under standard conditions for an addition reaction, for example by passing hydrogen bromide gas through a solution of the 4-bromo-1,1,2-difluorobut-1-ene in an inert solvent, optionally in the presence of a free radical generator, to give 1,4-dibromo-1,1,2-trifluorobutane. This compound is then treated with a debromofluorinating agent to give 4-bromo- 1,1-difluorobut-1-ene.

The present invention relates to an improved process for preparing 4-bromo-1,1-difluorobut-1-ene, and therefore also to an improved process for preparing end products which have 4-bromo-1,1-difluorobut-1-ene as an intermediate. Advantages of the process of the present invention include avoidance of the use of hazardous reagents, such as HF and LiAlHF.

According to one aspect of the present invention there is provided a process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the step of reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass and recovering the desired product therefrom.

The liquid reaction mass is preferably water; a water miscible, polar, non-reducible liquid, such as methanol and DMF; or a combination thereof.

Preferred defluorobrominating agents include zinc, magnesium and aluminium. Zinc is especially preferred. However the scope of the invention is not limited to the use of metals as defluorobrominating agents and other techniques such as electrochemical defluorochlorination processes may be used and are within the scope of the present invention.

When a metal is used the reaction is preferably carried out using at least a stoichiometric amount of the defluorobrominating agent. More preferably about 1.2 to about 1.5 moles of defluorobrominating agent are used per mole of

2,4-dibromo-1,1,1,-trifluorobut-1-ene. However, when the process is carried out electrochemically, less than stoichiometric amounts of the defluorobrominating agent can be used.

The reaction is preferably carried out at a pressure of about 1 atmosphere up to a temperature of about 100°C.

Preferably an initiator is used to start the reaction. Suitable initiators include iodine, concentrated HCl or even any residual metal from a preceding reaction.

According to another aspect of the present invention there is provided a process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the steps of

(a) reacting a 1,1,1-trifluorobutane-2,4-sulphonate, wherein the sulphonate is a leaving group, with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane; and

(b) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

In step (a)the sulfonate is preferably a tosylate or mesylate.

The reaction is preferably carried out at a temperature of at least about 100°C, more preferably from about 130°C to about 250°C, even more preferably, from about 130°C to about 200°C, at a pressure of about 1 atmosphere.

The reaction is preferably carried out in a polar aprotic solvent such as tetrahydrofuran, dimethylformamide, N-methylpyrrolidone, formamide, sulpholine and ketones.

The bromide source is preferably a neutral source of bromide, which is soluble in the solvent in which the step is preferably carried out, such as an alkali metal bromide, e.g. lithium bromide, sodium bromide or potassium bromide, calcium bromide, a quaternary ammonium bromide, and a quaternary pyrimidine bromide.

According to yet another aspect of the present invention there is provided a process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the steps of

(a) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluoro-butane-2,4-sulphonate;

(b) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane; and

(c) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

In step (a) the sulfonate is the tosylate or mesylate obtained by reaction with the appropriate sulphonyl chloride.

The reaction is preferably carried out in the presence of a solvent. The solvent is preferably a polar aprotic solvent such as those mentioned above.

The reaction is preferably carried out below the boiling point of the selected solvent at about 1 atmosphere.

In a preferred embodiment the reaction is carried out in the presence of a base, preferably an organic base such as a tertiary amine. Without wishing to be bound by any theory it is believed that the base aids in the formation of the alkoxy species.

According to a further aspect of the present invention there is provided a process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the steps of

(a) reacting ethyl trifluoromethyl-acetoacetate with a borohydride to form 1,1,1-trifluorobutane-1,2-diol;

(b) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate;

(c) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane;

(d) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

Step (a) may be carried out along the lines of the method described in J. Fluorine Chem. (1982), 20, 301-306, although, we have found that the amount of borohydride can be reduced over the amount described in the article. It will be appreciated that this is enviromentally advantageous.

In step (a) the borohydride is preferably sodium borohydride and the reaction is preferably carried out in a polar aprotic solvent such as those mentioned above. The solvent should not be reducible by the borohydride.

As previously mentioned, the present invention also relates to a process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane.

Misani et al in *J. Am. Chem. Soc.*, (1956), 78, 2801-2804 describes a failed attempt to prepare 2,4-dibromo-1,1,1-trifluorobutane by reacting 1,1,1-trifluorobutane-2,4-diol with phosphorus tribromide. The 2,4-dibromo-1,1,1-trifluorobutane was eventually prepared via ethyl β-bromo-γ,γ,γ-trifluorobutyrate and 1,1,1-trifluoro-2-bromo-4-butanol. Vasil'eva et al, *Izv. Akad. Nauk. SSSR, Ser Khim,* 1989 (11) 2558-62 report that 2,4-dibromo-1,1,1-trifluorobutane was obtained in mixture with other products by the reaction of dibromomethane with 3,3,3-trifluoroprop-1-ene. However these processes utilise hazardous or volatile reactants.

Thus, according to an aspect of the present invention there is provided a process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane comprising the step of

(a) reacting a 1,1,1-trifluorobutane-2,4-sulphonate, wherein the sulphonate is a leaving group, with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

According to another aspect of the present invention there is provide a process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane comprising the steps of

(a) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate; and

(b) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

According to a further aspect of the present invention there is provided a process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane comprising the steps of

(a) reacting ethyl trifluoromethyl-acetoacetate with a borohydride to form 1,1,1-trifluorobutane-1,2-diol;

(b) reacting 1,1,1-trifluorobutane-1,2-diol with a sulfonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate; and

(c) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

It will be appreciated that the preferred features mentioned in connection with the process of the present invention for preparing 4-bromo-1,1-difluorobut-1-ene are applicable to the corresponding step of the process of the present invention for preparing 2,4-dibromo-1,1,1-trifluorobutane.

Various preferred features and embodiments of the present invention will now be described by way of non-limiting examples with reference to the following Examples

EXAMPLE 1

This Example illustrates the preparation of 1,1,1-trifluorobutane- 2,4-diol.

17.2g sodium borohydride was suspended at room temperature in 400ml tetrahydrofuran, and 64g ethyl trifluoromethylacetoacetate was added dropwise over 100 minutes. During the addition the reaction mixture exothermed to 40°C. The mixture was refluxed for 2.5 hours and then cooled to 50°C. 240ml Methanol was then added, slowly at first to avoid foaming and then more rapidly as the hydrogen evolution rate diminished. The reaction mass was then refluxed for a further hour then the total solvent volume was reduced by distilling out 250ml of distillate. The mixture was cooled to room temperature and 400ml water and 75ml diethyl ether added, followed by stirring. The aqueous phase was separated off and extracted with a further 3 x 75ml diethyl ether. The ether extracts were combined and dried over sodium sulphate, then evaporated under reduced pressure to give 33g of a pale straw coloured viscous liquid containing 77% of the desired product by GLC.
nmr: CF_3CH (Mult. 4.2ppm); $OHCH_2$ (Mult. 1.85ppm); CH_2 (Mult. 3.9ppm)
[note: in $CDCl_3$ the OH protons were not clearly discernable]
^{19}F nmr: CF_3 (Sing. -81ppm).

EXAMPLE 2

This Example illustrates the preparation of 1,1,1-trifluorobutane- 2,4-bis-p-toluene sulphonate

32g Crude 1,1,1-trifluorobutane-2,4-diol was added with 51.7g p-toulenesulphonylchloride to 100ml tetrahydrofuran to produce a slurry. 45g Triethylamine was added dropwise over 45 minutes causing the reaction mixture to exotherm to 35°C and become thicker. GLC monitoring showed that after 6 hours the reaction was still incomplete. Over the following 13 days a further 2.0g p-toluene sulphonyl chloride was added in portions. GLC showed the reaction mass to be a mixture of the desired product (60%), monohydroxy tosylate (10%) and 2-chloro-4-tosylate (10%). The reaction mass was mixed with 300ml diethyl ether and filtered. The filter cake was washed with tetrahydrofuran. The filtrate was evaporated under reduced pressure to give 86g of a viscous amber coloured oil. 76g of the oil was dissolved in dichloromethane and washed with water. The mixture was dried to give 43g of the crude product. GLC MS showed the major peak to be 1,1,1-trifluorobutane-2,4-bis-p-toulene sulphonate of MWt 452. A minor quantity of 1,1,1-trifluoro-2-chlorobutane-4-tosylate of MWt 316 was also detected.

nmr: 7.85(D), 7.75(D), 7.40(D), 7.35(D), 4.95(CM), 4.18(CM), 4.05(CM), 2.45(S), 2.45(S), 2.20(CM), 2.08(CM).

^{19}F nmr: -77.28 (S)

EXAMPLE 3

This Example illustrates the preparation of 2,4-dibromo- 1,1,1-trifluorobutane.

Lithium bromide was charged into 120ml n-methylpyrrolidone and heated to 100°C producing a solution, this was cooled to 70°C and 40ml absolute ethanol added. The mixture was then reheated to 218°C whilst distilling out 40ml ethanol plus traces of water. The mixture was allowed to cool to 80°C and 30ml cyclohexane added. The mixture was again heated to 218°C whilst collecting the distillate. The mixture was allowed to cool and the previously prepared crude 1,1,1-trifluorobutane-2,4-bis-p-tosylate was added over 30 minutes, washed in with the aid of 2 x 20ml n-methylpyrrolidine. GLC analysis of the mixture after 1 hour at room temperature showed that all of the bis-tosylate had been converted to the 4-bromo-2-tosylate. The mixture was then heated to 90°C for approximately 2 hours and then allowed to cool to room temperature overnight. GLC analysis showed that conversion to the product was not complete. The mixture was heated to 130°C for 5 hours and at the end of this period the reaction was deemed complete. The reaction mass was allowed to cool to room temperature and drowned into water. The aqueous phase was extracted with 3 x 100ml of 30/40 petrol ether. The organic extracts were washed once with water, dried over sodium sulphate and the bulk of the petrol ether removed by flash

distillation at atmospheric pressure up to a head temperature of 40°C. The residue was distilled under reduced pressure using a water pump and the fraction up to 50°C collected.
Yield: 6.8g of a mixture containing by GLC product (78%) and
2-bromo-4-chloro-1,1,1-trifluorobutane (9.4%).
Product verified by GLC MS: Product: MWt 268; bromochloro: MWt 224
nmr: CH (CM 4.4ppm); $BrCH_2$ (CM 2.3ppm; CM 2.5ppm); CH_2 (M 3.5ppm; M 3.6ppm) Br.
^{19}F nmr: CF_3 (S -72.52ppm).

EXAMPLE 4

This Example illustrates the preparation of 4-bromo- 1,1-difluorobut-1-ene.

2.7g of 2,4-dibromo-1,1-trifluorobutane was charged to a flask containing 5ml water and 0.8g zinc metal powder. The mixture was heated to 70°C and two drops of concentrated hydrochloric acid and a crystal of iodine added to initiate the reaction. GLC monitoring of the reaction after 90 minutes at 70°C showed that the reaction had stooped, a further addition of 0.2g zinc metal powder and continuation of heating for a further 90 minutes were required to complete the reaction. The reaction flask was set for distillation, heating was increased and the distillate collected between 65° and 100°C. The distillate was dried with a small amount of sodium sulphate giving:
Yield: 0.95g of crude product (73.8% by GLC)
Product verified by GLC MS: product MWt 172; plus a small amount of
4-chloro-1,1-difluorobut-1-ene MWt 128
nmr: $BrCH_2$ (Trip. 3.37ppm); CH_2 (Mult. 2.55ppm) CH (Mult. 4.28ppm)
^{19}F: CF_2 (D -87.37, -87.43ppm); (d -89.17, -89.17ppm).

CLAIMS

1. A process for the preparation of 4-bromo-1,1-difluorobut-1-ene comprising the step of reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass and recovering the desired product therefrom.

2. A process for the preparation of 4-bromo-1,1-difluorobut-1-ene according to claim 1 comprising the steps of
(a) reacting a 1,1,1-trifluorobutane-2,4-sulphonate, wherein the sulphonate is a leaving group, with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane; and
(b) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

3. A process for the preparation of 4-bromo-1,1-difluorobut-1-ene according to claim 1 comprising the steps of
(a) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluoro-butane-2,4-sulphonate;
(b) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane; and
(c) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

4. A process for the preparation of 4-bromo-1,1-difluorobut-1-ene according to claim 1 comprising the steps of
(a) reacting ethyl trifluoromethyl-acetoacetate with a borohydride to form 1,1,1-trifluorobutane-1,2-diol;
(b) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate;
(c) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane;
(d) reacting 2,4-dibromo-1,1,1-trifluorobutane with a defluorobrominating agent in a liquid reaction mass.

5. A process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane comprising the step of reacting a 1,1,1-trifluorobutane- 2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

6. A process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane according to claim 5 comprising the steps of
(a) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate; and
(b) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

7. A process for the preparation of 2,4-dibromo-1,1,1-trifluorobutane according to claim 5 comprising the steps of
(a) reacting ethyl trifluoromethylacetoacetate with a borohydride to form 1,1,1-trifluorobutane-1,2-diol;
(b) reacting 1,1,1-trifluorobutane-1,2-diol with a sulphonyl halide to form a corresponding 1,1,1-trifluorobutane-2,4-sulphonate; and
(c) reacting the 1,1,1-trifluorobutane-2,4-sulphonate with a source of bromide to produce 2,4-dibromo-1,1,1-trifluorobutane.

8. A process according to claim 1 wherein the defluorobrominating agent is selected from metallic zinc, aluminium and magnesium.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C21/18 C07C17/23 C07C19/14 C07C17/093

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 04727 A (ZENECA LTD) 16 February 1995 see claims 8-10	1,8
A	GB 2 270 688 A (ZENECA LTD) 23 March 1994 cited in the application see page 40 - page 41	7
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

information on patent family members

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